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Scientific and Technical Information Center

SEARCH REQUEST FORM

Date: 3/3/2003 Requester's Full Name: Sabiha Hoque Examiner #: 74414

Art Unit: 1616 Phone (305) 3910 Serial Number: 09/971,960

Results Format Preferred (circle): PAPER DISK E-MAIL

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To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: 5-membered Heterocycles as inhibitors of Leucocyte Adhesion & as VLA antagonist

Inventors (please provide full names): Ulrich Stilz et al

Earliest Priority Date: 11/15/96 (German Priority 196-47-380.2)

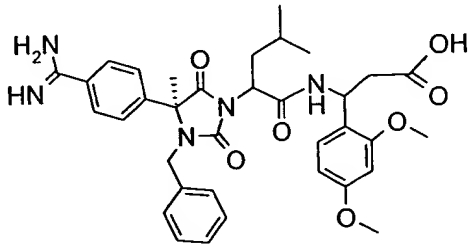
Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known.

For Sequence Searches Only *Please include all pertinent information (parent, grandchild, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search the compds of formula (I), claim 21 for a method of suppressing inflammation and antagonising VLA-4. & Preparation (No Heterocycles)

Example 53:
(R,S)-3-((R,S)-2-((S)-4-(4-(Amino-imino-methyl)phenyl)-3-benzyl-4-methyl-2,5-dioxoimidazolidin-1-yl)-2-(2-methylpropyl)acetylamino)-3-(2,4-dimethoxyphenyl)propionic acid



Elected Species

No Hetero to be Searched

Please see attached Cl 21 + 22

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Searcher: STN D

Searcher Phone #:

Searcher Location:

Date Searcher Picked Up: 3

Date Completed: 3-13

Searcher Prep & Review Time: 20

Type of Search

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___ AA Sequence (#)

1 Structure (#)

___ Bibliographic

___ Litigation

___ Fulltext

Other

Vendors and Cost

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___ WWW/Internet

___ In-house sequence systems (list)

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Dear Examiner,

You can help us in our efforts to get searches back to you in a timely manner by including your art unit and room number on all searches you submit to the STIC.

Thanks from the STIC-Biotech/Chemistry Library

BOX AF – EXPEDITED HANDLING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 026083/0138

In re patent application of

Hans Ulrich Stilz et al.

Group Art Unit: 1616

Serial No. 08/971,960

Examiner: S. Qazi

Filed: November 17, 1997

For: 5-MEMBERED RING HETEROCYCLES AS INHIBITORS OF LEUCOCYTE ADHESION AND AS VLA-4 ANTAGONISTS

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. § 1.116

Assistant Commissioner for Patents
Washington, D.C. 20231
BOX AF

Sir:

In response to the outstanding Office Action mailed May 14, 1999, please amend the above-identified application as follows:

IN THE CLAIMS:

Please cancel claims 1-20 and 25-38 without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to their subject matter.

Please rewrite the following claims:

21. (amended) A method for suppressing inflammation comprising administering to a subject in need thereof an effective amount of [the preparation as claimed in claim 1] a preparation comprising an effective amount of at least one compound of the formula I:

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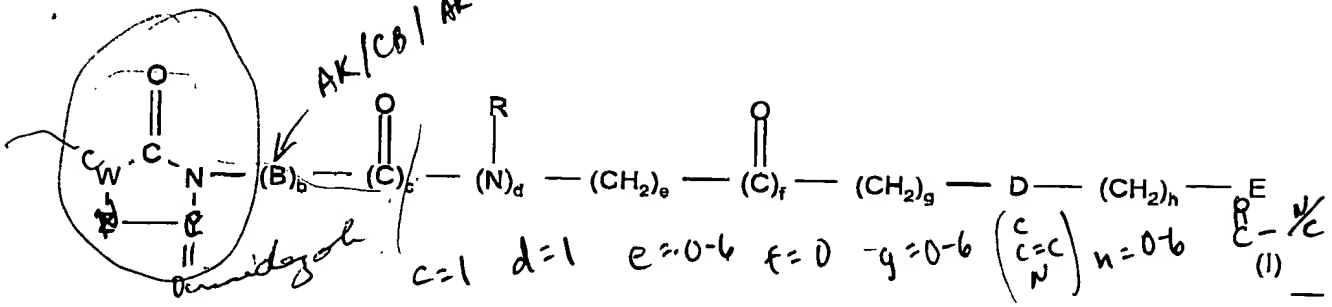

in which

W is R^1-A-C(R^{13})<;

Y is a carbonyl;

Z is N(R^0);

A is a bivalent radical from the group consisting of (C_1-C_6)-alkylene, (C_3-C_7)-cycloalkylene, phenylene, phenylene-(C_1-C_6)-alkyl, (C_1-C_6)-alkylenephenyl, phenylene-(C_2-C_6)-alkenyl or a bivalent radical of a 5- or 6-membered saturated or unsaturated ring which can contain 1 or 2 nitrogen atoms and can be mono- or disubstituted by (C_1-C_6)-alkyl or doubly bonded oxygen or sulfur;

B is a bivalent radical from the group consisting of (C_1-C_6)-alkylene, (C_2-C_6)-alkenylene, phenylene, phenylene-(C_1-C_3)-alkyl, (C_1-C_3)-alkylenephenyl, where the bivalent (C_1-C_6)-alkylene radical can be unsubstituted or substituted by a radical from the group consisting of (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_3-C_{10})-cycloalkyl, (C_3-C_{10})-cycloalkyl-(C_1-C_6)-alkyl, optionally substituted (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_6)-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl and heteroaryl-(C_1-C_6)-alkyl optionally substituted in the heteroaryl radical;

D is C(R^2)(R^3), N(R^3) or CH=C(R^3);

E is R^{10}CO;

R is hydrogen, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, optionally substituted (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical;

R^0 is hydrogen, (C_1-C_8)-alkyl, (C_3-C_{12})-cycloalkyl, (C_3-C_{12})-cycloalkyl-(C_1-C_8)-alkyl, (C_6-C_{12})-bicycloalkyl, (C_6-C_{12})-bicycloalkyl-(C_1-C_8)-alkyl, (C_6-C_{12})-tricycloalkyl, (C_6-C_{12})-tricycloalkyl-(C_1-C_8)-alkyl, optionally substituted (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl, heteroaryl-(C_1-

C_8)-alkyl optionally substituted in the heteroaryl radical, CHO, (C_1-C_8)-alkyl-CO, (C_3-C_{12})-cycloalkyl-CO, (C_3-C_{12})-cycloalkyl-(C_1-C_8)-alkyl-CO, (C_6-C_{12})-bicycloalkyl-CO, (C_6-C_{12})-bicycloalkyl-(C_1-C_8)-alkyl-CO, (C_6-C_{12})-tricycloalkyl-CO, (C_6-C_{12})-tricycloalkyl-(C_1-C_8)-alkyl-CO, optionally substituted (C_6-C_{14})-aryl-CO, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl-CO optionally substituted in the aryl radical, optionally substituted heteroaryl-CO, heteroaryl-(C_1-C_8)-alkyl-CO optionally substituted in the heteroaryl radical, (C_1-C_8)-alkyl-S(O)$_n$, (C_3-C_{12})-cycloalkyl-S(O)$_n$, (C_3-C_{12})-cycloalkyl-(C_1-C_8)-alkyl-S(O)$_n$, (C_6-C_{12})-bicycloalkyl-S(O)$_n$, (C_6-C_{12})-bicycloalkyl-(C_1-C_8)-alkyl-S(O)$_n$, (C_6-C_{12})-tricycloalkyl-S(O)$_n$, (C_6-C_{12})-tricycloalkyl-(C_1-C_8)-alkyl-S(O)$_n$, optionally substituted (C_6-C_{14})-aryl-S(O)$_n$, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl-S(O)$_n$ optionally substituted in the aryl radical, optionally substituted heteroaryl-S(O)$_n$ or heteroaryl-(C_1-C_8)-alkyl-S(O)$_n$, optionally substituted in the heteroaryl radical, where n is 1 or 2;

R^1 is X-NH-C(=NH)-$(CH_2)_p$ or X^1-NH-$(CH_2)_p$, where p is 0, 1, 2 or 3;

X is hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_{18})-alkylcarbonyloxy-(C_1-C_6)-alkoxycarbonyl, optionally substituted (C_6-C_{14})-arylcarbonyl, optionally substituted (C_6-C_{14})-aryloxycarbonyl, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl which can also be substituted in the aryl radical, $(R^8O)_2P(O)$, cyano, hydroxyl, (C_1-C_6)-alkoxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy which can also be substituted in the aryl radical, or amino;

X^1 has one of the meanings of X or is R'-NH-C(=N-R''), where R' and R'' independently of one another have the meanings of X;

R^2 is hydrogen, (C_1-C_8)-alkyl, optionally substituted (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical or (C_3-C_8)-cycloalkyl;

R^3 is hydrogen, (C_1-C_8)-alkyl, optionally substituted (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical, (C_3-C_8)-cycloalkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_2-C_8)-alkenylcarbonyl, (C_2-C_8)-alkynylcarbonyl, pyridyl, $R^{11}NH$, R^4CO, $COOR^4$, $CON(CH_3)R^{14}$, $CONHR^{14}$, $CSNHR^{14}$, $COOR^{15}$, $CON(CH_3)R^{15}$ or $CONHR^{15}$;

R^4 is hydrogen or (C_1-C_{28})-alkyl which can optionally be mono- or polysubstituted by identical or different radicals $R^{4'}$; $R^{4'}$ is hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-((C_1-C_{18})-alkyl)aminocarbonyl, amino-(C_2-C_{18})-alkylaminocarbonyl, amino-(C_1-C_3)-

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alkylphenyl-(C_1-C_3)-alkylaminocarbonyl, (C_1-C_{18})-alkylcarbonylamino-(C_1-C_3)-alkylphenyl-(C_1-C_3)-alkylaminocarbonyl, (C_1-C_{18})-alkylcarbonylamino-(C_2-C_{18})-alkylaminocarbonyl, (C_6-C_{14})-aryl-(C_1-C_8)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C_1-C_{18})-alkoxy, (C_1-C_{18})-alkoxycarbonyl, optionally substituted (C_3-C_8)-cycloalkyl, halogen, nitro, trifluoromethyl or the radical R^5;

R^5 is optionally substituted (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical, a mono- or bicyclic 5- to 12-membered heterocyclic ring which can be aromatic, partially hydrogenated or completely hydrogenated and which can contain one, two or three identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur, a radical R^5 or a radical R^6CO-, where the aryl radical and, independently thereof, the heterocyclic radical can be mono- or polysubstituted by identical or different radicals from the group consisting of (C_1-C_{18})-alkyl, (C_1-C_{18})-alkoxy, halogen, nitro, amino and trifluoromethyl;

R^6 is R^7R^8N, R^7O or R^7S or an amino acid side chain, a natural or unnatural amino acid, imino acid, optionally N-(C_1-C_8)-alkylated or N-((C_6-C_{14})-aryl-(C_1-C_8)-alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to -NH-CH_2-, and their esters and amides, where hydrogen or hydroxymethyl can optionally stand in place of free functional groups and/or where free functional groups can be protected by protective groups customary in peptide chemistry;

R^7 is hydrogen, (C_1-C_{18})-alkyl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl, (C_1-C_{18})-alkylcarbonyl, (C_1-C_{18})-alkoxycarbonyl, (C_6-C_{14})-arylcarbonyl, (C_6-C_{14})-aryl-(C_1-C_8)-alkylcarbonyl or (C_6-C_{14})-aryl-(C_1-C_{18})-alkyloxycarbonyl, where the alkyl groups can optionally be substituted by an amino group and/or where the aryl radicals can be mono- or polysubstituted, preferably monosubstituted, by identical or different radicals from the group consisting of (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, halogen, nitro, amino and trifluoromethyl, or is a natural or unnatural amino acid, imino acid, optionally N-(C_1-C_8)-alkylated or N-((C_6-C_{14})-aryl-(C_1-C_8)-alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to -NH-CH_2-;

R^8 is hydrogen, (C_1-C_{18})-alkyl, optionally substituted (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_8)-alkyl which can also be substituted in the aryl radical;

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R^9 is hydrogen, aminocarbonyl, (C_1-C_{18})-alkylaminocarbonyl, (C_3-C_8)-cycloalkylaminocarbonyl, optionally substituted (C_6-C_{14})-arylaminocarbonyl, (C_1-C_{18})-alkyl, optionally substituted (C_6-C_{14})-aryl or (C_3-C_8)-cycloalkyl;

R^{10} is hydroxyl, (C_1-C_{18})-alkoxy, (C_6-C_{14})-aryl-(C_1-C_8)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C_6-C_{14})-aryloxy, amino or mono- or di-$((C_1-C_{18})$-alkyl)amino;

R^{11} is hydrogen, (C_1-C_{18})-alkyl, $R^{12}CO$, optionally substituted (C_6-C_{14})-aryl-$S(O)_2$, (C_1-C_{18})-alkyl-$S(O)_2$, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical or $R^9NHS(O)_2$;

R^{12} is hydrogen, (C_1-C_{18})-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, optionally substituted (C_6-C_{14})-aryl, (C_1-C_{18})-alkoxy, (C_6-C_{14})-aryl-(C_1-C_8)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C_6-C_{14})-aryloxy, amino or mono- or di-$((C_1-C_{18})$-alkyl)amino;

R^{13} is hydrogen, (C_1-C_6)-alkyl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl optionally substituted in the aryl radical or (C_3-C_8)-cycloalkyl;

R^{14} is hydrogen or (C_1-C_{28})-alkyl which can optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-$((C_1-C_{18})$-alkyl)-aminocarbonyl, amino-(C_2-C_{18})-alkylaminocarbonyl, amino-(C_1-C_3)-alkylphenyl-(C_1-C_3)-alkylaminocarbonyl, (C_1-C_{18})-alkylcarbonylamino-(C_1-C_3)-alkylphenyl-(C_1-C_3)-alkylaminocarbonyl, (C_1-C_{18})-alkylcarbonyl-amino-(C_2-C_{18})-alkylaminocarbonyl, (C_6-C_{14})-aryl-(C_1-C_8)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C_1-C_{18})-alkoxy, (C_1-C_{18})-alkoxycarbonyl, optionally substituted (C_3-C_8)-cycloalkyl, $HOS(O)_2$-(C_1-C_3)-alkyl, $R^9NHS(O)_2$-(C_1-C_3)-alkyl, $(R^{11}O)_2P(O)$-(C_1-C_3)-alkyl, tetrazolyl-(C_1-C_3)-alkyl, halogen, nitro, trifluoromethyl and R^5;

R^{15} is R^{16}-(C_1-C_6)-alkyl or R^{16};

R^{16} is a 6- to 24-membered bicyclic or tricyclic radical which is saturated or partially unsaturated and which can also contain one to four identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur and which can also be substituted by

one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl and oxo;

b, c, and d are 1;

e is 0, 1, 2, 3, 4, 5 or 6;

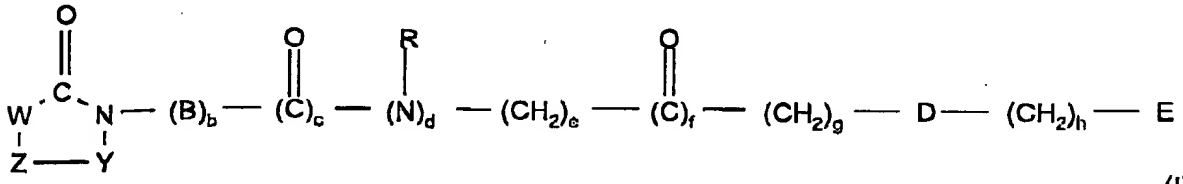
f is 0;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0, 1, 2, 3, 4, 5 or 6;

in all their stereoisomeric forms and mixtures thereof in any ratio, and of their physiologically tolerable salts.

22. (amended) A method for antagonizing VLA-4 comprising administering to a subject in need thereof an effective amount of [the preparation as claimed in claim 1] a preparation comprising an effective amount of at least one compound of the formula I:



(I)

in which

W is R^1-A-C(R^{13})<;

Y is a carbonyl;

Z is N(R^0);

A is a bivalent radical from the group consisting of (C_1-C_6)-alkylene, (C_3-C_7)-cycloalkylene, phenylene, phenylene-(C_1-C_6)-alkyl, (C_1-C_6)-alkylenephenyl, phenylene-(C_2-C_6)-alkenyl or a bivalent radical of a 5- or 6-membered saturated or unsaturated ring which can contain 1 or 2 nitrogen atoms and can be mono- or disubstituted by (C_1-C_6)-alkyl or doubly bonded oxygen or sulfur;

B is a bivalent radical from the group consisting of (C_1-C_6)-alkylene, (C_2-C_6)-alkenylene, phenylene, phenylene-(C_1-C_3)-alkyl, (C_1-C_3)-alkylenephenyl, where the bivalent (C_1-C_6)-alkylene radical can be unsubstituted or substituted by a radical from the group consisting